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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,453	07/18/2006	Matthew David Osborne	BJS-620-412	4519

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EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,453	OSBORNE ET AL.	
	Examiner	Art Unit	
	MARIA MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,9,10,13-16,33,36,41 and 45-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,9,10,13-16,33,36,41 and 45-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/2/11 has been entered.

Claims 1, 4, 9, 10, 13-16, 33, 36, 41 and 45-50 are pending in this application.

Claim Objections

Claims 1, 45 and 49 are objected to because of the following informalities: In claim 1, "in vitro" should be italicized.

As well, the medium is not to contain any of transferrin, a lipophilic chelator, a synthetic nitrogen- containing chelator or a lipophilic synthetic nitrogen containing chelator. This phrase, however, can appear to mean that it cannot contain any single compound because of the "or". To avoid this interpretation, it would be clearer to recite, --any of a transferrin, a lipophilic chelator, a synthetic nitrogen- containing chelator and a lipophilic synthetic nitrogen containing chelator--.

Claim 45 depends from claim 33 whereas it appears it should be dependent from claim 41.

Claim 49 should be amended to recite each of the products in the singular form preceded by articles for proper format as the claim requires use of "a cell product" or "the cell product".

Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 9, 10, 13-16, 33, 36, 41 and 45-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Field et al (US 6,593,140; see entire document) in view of Gorfien et al (US 20060148074; see entire document). **This rejection is maintained for reasons below.**

Applicants claim a method of culturing myeloma cells in media lacking transferring, lacking lipophilic chelators and lacking synthetic and/or lipophilic nitrogen containing chelators and in the presence of ferric ammonium citrate.

Myeloma cells were cultured *in vitro* in suspension culture in media lacking transferrin, lipophilic chelators and nitrogen containing chelators but in the presence of ferric chloride-sodium citrate (see e.g. ¶ 0094 and example 5, line 29-31). Iron is in the concentration of **0.28 mg/L to 11 mg/L** (see e.g. ¶ 0113). As evidenced by the instant specification, the concentration of 1.25 mg/L of ferric ammonium citrate is about 0.2 mg/L of iron. Hence, the iron concentration is about 0.03 mg/L. The media was serum-free see example 2 and as depicted in figure 1, the control cultures do not contain chelators.

> [0153] In a preferred embodiment, the replacement medium of the present invention is used to grow CHO cells in suspension culture. In another preferred embodiment, the replacement medium of the present invention is used to grow hybridoma cells in suspension culture. In yet another preferred embodiment, the replacement medium of the present invention can be used to culture NS/O myeloma cells

in suspension culture. If NS/O myeloma cells are cultured, the replacement 1.times. medium of the present invention can be supplemented with a lipid mixture supplement (see Table 3).

The replacement media also most explicitly contains iron in place of transferrin.

[0112] In the replacement media of the invention, any basal media may be used. Such basal media may contain one or more amino acids, one or more vitamins, one or more inorganic salts, one or more buffer salts, and one or more lipids. In accordance with the invention, **transferrin is replaced with iron or an iron-containing compound a**nd/or insulin is replaced with zinc or a zinc containing compound. Preferably, iron chelate compounds are used in accordance with the invention

The disclosure of Fields et al states that the cells do not survive after 48 hours.

In the absence of either tropolone or transferrin but in the presence of 0.2 mg/l ferric ammonium citrate myeloma cells failed to thrive and died within 48 hours.

To this end, Gorfien teaches media for culturing myeloma wherein the iron concentration is between 0.28 and 11 mg/L. Hence, the iron concentration would be about 1.75-68.75 mg/L of ferric ammonium citrate. Gorfien teaches that the iron can be any number of compounds. It is unclear that FAC does not fall into the category of ferric citrate chelators.

[0113] Fe.sup.2+ and/or Fe.sup.3+ chelate compounds which may be used include but are not limited to compounds containing an Fe.sup.2+ and/or Fe.sup.3+ salt and a chelator such as ethylenediaminetetraacetic acid (EDTA), ethylene glycol-bis(.beta.-aminoethyl ether)-N,N,N,N'-tetraacetic acid (EGTA), deferoxamine mesylate, dimercaptopropanol, diethylenetriaminepentaacetic acid (DPTA), and trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (CDTA). For example, the iron chelate compound may be **a ferric citrate chelate** or a ferrous sulfate chelate. Preferably, the iron chelate compound used is ferrous sulphate.7H.sub.2O EDTA (FeSO.sub.40.7H.sub.2O EDTA, e.g., Sigma F0518, Sigma, St. Louis, Mo.). In the medium of the present invention, the concentration of Fe.sup.2' and/or Fe.sup.3+ can be optimized using only routine experimentation. **Typically, the concentration of Fe.sup.2+ and/or Fe.sup.3+ in the 1.times medium of the present invention can be about 0.00028 to 0.011 g/L.** Preferably, the concentration of iron is about 0.0011 g/L.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use ferric ammonium citrate as taught by Field et al in the media taught by Gorfien et al because Gorfien et al teach that it is within the ordinary skill of the art to use particular levels of iron to culture myeloma cells and because Fields et al teach that it is within the ordinary skill of the art to use ferric ammonium citrate as a source of iron. In KSR International Co. v. Teleflex lnc., 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that obviousness in part is predicated on use of particular known techniques that are recognized as part of the ordinary capabilities of one skilled in the art. In the instant case, Gorfien and Field et al are both directed at methods of culturing myeloma cells. The combination of the two represents the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (Id. At 1395.) Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to applicants' arguments

The 103 rejection is based on the teachings of Gorfien et al who teaches the instant method but does not provide the details of the iron chelator. Specifically, Gorfien et al teaches growth of myeloma cells in media that lacks transferrin, a lipophilic chelator, a synthetic

nitrogen-containing chelator or a lipophilic synthetic nitrogen containing chelator. The cells are grown under conditions of agitation in shaker rollers.

> [0166] For suspension cultivation, cells are typically suspended in the present culture media and introduced into a culture vessel that facilitates cultivation of the cells in suspension, such as a spinner flask, perfusion apparatus, or bioreactor (see Freshney, R. I., Culture of Animal Cells: A Manual of Basic Technique, New York: Alan R. Liss, Inc., pp. 123-125 (1983)). Ideally, agitation of the media and the suspended cells will be minimized to avoid denaturation of media components and shearing of the cells during cultivation.

> [0158] 293 human embryonic kidney cells and HeLaS3 cells are particularly preferred for growth in the suspension medium of the present invention. Chinese hamster ovary (CHO) cells, NS/O cells, and hybridoma cells are particularly preferred for growth in the replacement medium of the present invention. Especially preferred are CHO cells.

The replacement media is media that uses an iron chelate. To this end, Gorfien et al teaches use of iron at a concentration of 0.28mg/l to 11 mg/l. The only aspect of Gorfien et al that is lacking is naming as an iron source ferric ammonium citrate. In fact, in Gorfien et al, the exact particulars of the replacement compound do not appear to be limiting. Gorfien et al appreciates that there are a number of iron chelators that can be used.

> [0113] Fe.sup.2+ and/or Fe.sup.3+ chelate compounds which may be used include but are not limited to compounds containing an Fe.sup.2+ and/or Fe.sup.3+ salt and a chelator such as ethylenediaminetetraacetic acid (EDTA), ethylene glycol-bis(.beta.-aminoethyl ether)-N,N,N,N'-tetraacetic acid (EGTA), deferoxamine mesylate, dimercaptopropanol, diethylenetriaminepentaacetic acid (DPTA), and trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (CDTA). For example, the iron chelate compound may be a ferric citrate chelate or a ferrous sulfate chelate. Preferably, the iron chelate compound used is ferrous sulphate.7H.sub.2O EDTA (FeSO.sub.4O.7H.sub.2O EDTA, e.g., Sigma F0518, Sigma, St. Louis, Mo.). In the medium of the present invention, the concentration of Fe.sup.2' and/or Fe.sup.3+ can be optimized using only routine experimentation. Typically, the concentration of Fe.sup.2+ and/or Fe.sup.3+ in the 1.times medium of the present invention can be about 0.00028 to 0.011 g/L. Preferably, the concentration of iron is about 0.0011 g/L.

A review of the art demonstrates that iron replacements comprise a number of formulations that are used interchangeably. Both ferric citrate and ferric ammonium citrate are ferric carboxylates that are used interchangeably in a number of cell culture mediums e.g. 5,316,938, col 5 and US 20050069979 ¶ 0044. The methods of Gorfien look to the art for sources of iron that are replacement components. Hence, Fields et al provides description of those items encompassed by but not explicitly disclosed by Gorfien et al. Specifically, Fields et al teach the use of FAC as an iron chelator for growth of cells including myeloma cells. One would looking at the methods of Gorfien et al be motivated to use FAC as Gorfien et al directs one to ferric citrate chelators in the methods of growing myeloma cells and because Fields et al teaches use of FAC in growth methods.

Applicants traverse the rejection under 35 USC 103 for the following reasons. Applicants argue that hybridoma cells when cultured under agitation and increased FAC are destroyed and one would not raise the concentration of FAC for myeloma cells as one would expect the same results for myeloma cells. The failures of Fields et al are not demonstrated to be due to use of FAC but most presumably by differences in the methods of Fields et al and Gorfien et al. Applicants point out that Gorfien found it essential to mitigate the known toxic effects of high iron by using beta glycerophosphate. However, the use of beta-glycerophosphate is not excluded by the instant claims. Gorfien seeks to improve methods of culturing cells such as CHO, hybridoma and myeloma cells, (¶ 0153 and abstract). Some of the improvements are taught in the following passages.

> 0153] In a preferred embodiment, the replacement medium of the present invention is used to grow CHO cells in suspension culture. In another preferred embodiment, the

replacement medium of the present invention is used to grow hybridoma cells in suspension culture. In yet another preferred embodiment, the replacement medium of the present invention can be used to culture NS/O myeloma cells in suspension culture. If NS/O myeloma cells are cultured, the replacement 1.times. medium of the present invention can be supplemented with a lipid mixture supplement (see Table 3).

The present invention provides a cell culture medium formulation that supports the in vitro cultivation, particularly in suspension, of mammalian cells, particularly epithelial cells and fibroblast cells, and methods for cultivating mammalian cells in suspension in vitro using these media. The media comprise a basal medium and a polyanionic or polyanionic compound, preferably a polysulfonated or polysulfated compound, and more preferably dextran sulfate. The present invention also provides chemically defined, protein-free eukaryotic cell culture media comprising an iron chelate and zinc, which is capable of supporting the growth (and particularly the high-density growth of mammalian cells) in suspension culture, increasing the level of expression of recombinant protein in cultured cells, and/or increasing virus production in cultured cells.

[

[0117] The inclusion of polyanionic or polycationic compounds (preferably, dextran sulfate) in the present media inhibits cell aggregation; thus, unlike traditional serum-free media in which suspension cells tend to aggregate or form clumps, the present media promote the cultivation of single cells in suspension. The ability to cultivate cells under these suspension culture conditions provides for rapid subculturing and high-density culture, which are advantageous for applications in which mammalian cells are used to produce a variety of products such as in the biotechnology industry, as described below. Furthermore, since the present media are serum-free and low-protein or protein-free, the media may be used for rapid production and isolation of biologicals (e.g., viruses, recombinant polypeptides, etc.), and in assays measuring the binding and/or activity of a variety of ligands such as proteins, hormones, synthetic organic or inorganic drugs, etc., on mammalian cells in vitro.

[0144] For the 1.times. medium to be effective for culturing NS/O myeloma cells, a lipid mixture supplement may need to be added to the 1.times. medium. The lipid supplement formulation of Table 3 can be added to the 1.times. medium prior to filter sterilization.

Hence, as a whole, Gorfien et al teach methods of improving cell culture and in looking to the art for acceptable iron chelators, a number of teachings suggesting the desirability of FAC would direct a person of skill in the art to the instant invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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